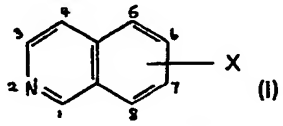
(12) UK Patent Application (19) GB (11) 2 065 121 A

(21) Application No 8039322
(22) Date of filing 8 Dec 1980
(30) Priority data
(31) 79/43041
(32) 13 Dec 1979
(33) United Kingdom (GB)
(43) Application published
24 Jun 1981
(51) INT CL³
C07D 217/02 A61K 31/44
C07D 401/12 409/12
(C07D 401/12 213/60
217/02 231/20 257/04)
(C07D 409/12 333/38)
(52) Domestic classification
C2C 1401 1464 1510
1530 1535 213 215 220
22Y 244 246 247 248 250
251 252 254 258 25Y 280
281 282 28X 29X 29Y
305 30Y 321 326 32Y 341
342 34Y 350 351 352 364
366 367 368 36Y 385 388
40Y 43X 45X 45Y 490
49Y 500 50Y 512 51X
531 54X 574 604 620
624 625 626 628 62X
62Y 650 656 658 65X
662 666 668 672 678 682
69Y 70X 71X 761 768
770 802 80Y AA BB BK KD
KP KQ LF MB SJ TA TW
WK
(56) Documents cited
None
(58) Field of search
C2C
(71) Applicant
Pfizer Limited,
Ramsgate Road,
Sandwich, Kent
(72) Inventors
Ian Thompson Barnish,
Peter Edward Cross,
Roger Peter Dickinson
(74) Agent
D. J. Wood,
Pfizer Limited, Ramsgate
Road, Sandwich, Kent

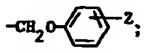
(54) Isoquinoline Derivatives

(57) Isoquinolines having thromboxane synthetase inhibiting activity of the general formula:—

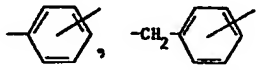


(I)

wherein X, which is attached to the 5-, 6-, 7- or 8- position, is a group of the formula —O—Y—Z or



Y is —$(CH_2)_n$— wherein n is 1, 2, 3 or 4, or a group of the formula;—



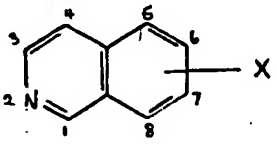
or —CH_2—(Het)—; Het represents a 5 or 6 membered aromatic heterocyclic ring linked to Z by a ring carbon atom;
Z is —CO_2R^1, —$CONHR^2$, —$CON(R^3)_2$, —NHR^4, —$NHCONHR^5$, —CN, 5-tetrazolyl, 5-oxo-2-pyrazolin-1-yl or 3-methyl-5-oxo-2-pyrazolin-1-yl, with the proviso that when Y is —CH_2—(Het)—, Z may also be C_1—C_4 alkyl, but may not be —NHR^4 or —$NHCONHR^5$;
R^1 is H or C_1—C_4 alkyl;
R^2 is H, C_1—C_4 alkyl, C_2—C_4 alkanoyl, aroyl, C_1—C_4 alkyl-sulphonyl, arylsulphonyl, aryl, aralkyl, or a 5 or 6 membered aromatic heterocyclic ring optionally substituted by one or two C_1—C_4 alkyl, C_1—C_4 alkoxy, halogen or CF_3 groups;
each R^3 is C_1—C_4 alkyl or two groups R_3 together with the nitrogen atom to which they are attached form a pyrrolidino or piperidino group;
R^4 is H, C_1—C_4 alkyl, C_2—C_4 alkanoyl, C_1—C_4 alkylsulphonyl, or (C_1—C_4 alkoxy)carbonyl:
and R^5 is C_1—C_4 alkyl or aryl:
and the pharmaceutically acceptable acid addition salts thereof;
pharmaceutical compositions containing them, and processes for their preparation.

SPECIFICATION

Isoquinoline Derivatives

This invention relates to isoquinoline derivatives and in particular to certain isoquinolines having a substituent in the 5-, 6, 7- or 8- position. Such compounds are able to selectively inhibit the action of the thromboxane synthetase enzyme without significantly inhibiting the action of the prostacyclin synthetase or cyclo-oxygenase enzymes. The compounds are thus useful in, for example, the treatment of thrombosis, ischaemic heart disease, stroke, transient ischaemic attack, migraine and the vascular complications of diabetes.

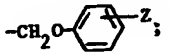
According to the invention there are provided compounds of the general formula:—



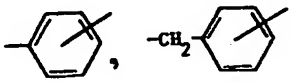
— (I)

wherein

X, which is attached to the 5-, 6-, 7- or 8- position, is a group of the formula —O—Y—Z or



Y is $—(CH_2)_n—$ wherein n is 1, 2, 3 or 4, or a group of the formula:—



Het represents a 5 or 6 membered aromatic heterocyclic ring linked to Z by a ring carbon atom;

Z is $—CO_2R^1$, $—CONHR^2$, $—CON(R^3)_2$, $—NHR^4$, $—NHCONHR^5$, —CN, 5-tetrazolyl, 5-oxo-2-pyrazolin-1-yl or 3-methyl-5-oxo-2-pyrazolin-1-yl, with the proviso that when Y is $—CH_2—$(Het)—, Z may also be $C_1—C_4$ alkyl, but may not be $—NHR^4$ or $—NHCONHR^5$;

R^1 is H or $C_1—C_4$ alkyl;

R^2 is H, $C_1—C_4$ alkyl, $C_2—C_4$ alkanoyl, aroyl, $C_1—C_4$ alkylsulphonyl, arylsulphonyl, aryl, aralkyl, or a 5 or 6 membered aromatic heterocyclic ring optionally substituted by one or two $C_1—C_4$ alkyl, $C_1—C_4$ alkoxy, halogen or CF_3 groups;

each R^3 is $C_1—C_4$ alkyl or two groups R^3 together with the nitrogen atom to which they are attached form a pyrrolidino or piperidino group;

R^4 is H, $C_1—C_4$ alkyl, $C_2—C_4$ alkanoyl, $C_1—C_4$ alkylsulphonyl, or ($C_1—C_4$ alkoxy)carbonyl; and

R^5 is $C_1—C_4$ alkyl or aryl;

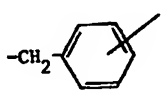
and the pharmaceutically acceptable acid addition salts thereof.

The 5 or 6 membered aromatic heterocyclic rings may contain as a hetero atom a single nitrogen, oxygen or sulphur atom, or a nitrogen atom together with a further nitrogen, oxygen or a sulphur atom, and thus may be for example pyridyl, thiazolyl, furyl, pyrazolyl, isoxazolyl, or pyrimidinyl.

The preferred aryl, aroyl and aralkyl groups are, respectively, phenyl, benzoyl and benzyl, all optionally ring substituted by one or two substituents selected from $C_1—C_4$ alkyl, $C_1—C_4$ alkoxy halogen and CF_3.

Pharmaceutically acceptable acid addition salts of the compounds of the invention are salts with acids containing pharmaceutically acceptable anions, e.g. the hydrochloride, hydrobromide, sulphate or bisulphate, phosphate or acid phosphate, acetate, maleate, fumarate, lactate, tartrate, citrate, gluconate, succinate and *p*-toluene sulphonate salts.

In one aspect of the invention X is in the 5- position and is —O—Y—Z; Y is $—(CH_2)_n—$ where n is as defined in claim 1 or a group of the formula:

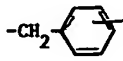


or $—CH_2—$(Het)—; and Z and "Het" are as for formula (I).

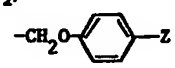
In the preferred compounds X is in the 5- or 7- position; and Y is selected from:

(a) $—(CH_2)_nZ$ wherein n is 1, 2 or 3 and Z is $—CO_2H$, $—CO_2$ ($C_1—C_4$ alkyl), $—CONH_2$, $—NH_2$, —CN, —NHCONH ($C_1—C_4$ alkyl), —NHCONH.Phenyl, $—NH_2SO_2$($C_1—C_4$ alkyl), 5-tetrazolyl, or 3-methyl-5-oxo-2-pyrazolin-1-yl;

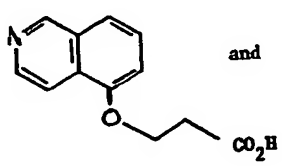
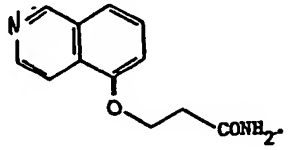
(b)  wherein Z is —CN, —$CONH_2$ or —COOH;

(c)  wherein Z is —CN, —$CONH_2$, —COOH or —CONH(2-pyridyl);

(d) —CH_2—(Het)—Z wherein "Het" is pyridyl or thienyl and Z is —COOH, —$COO(C_1$—C_4 alkyl) or —$CONH_2$; and

(e)  wherein Z is —COOH or —$COO(C_1$—C_4 alkyl).

The most preferred individual compounds are:—

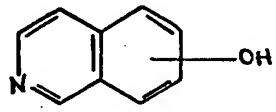
 and 

In this specification "halogen" indicates fluorine, chlorine, bromine or iodine. Alkyl and alkoxy groups having 3 or more carbon atoms and alkanoyl groups having 4 carbon atoms may be straight or branched chain.

The invention also includes a pharmaceutical composition comprising a compound of the formula (I), or a pharmaceutically acceptable acid addition salt thereof, together with a pharmaceutically acceptable diluent or carrier.

The compounds of the invention may be prepared by a number of different routes, including the following:—

(1) In one process the compounds of the formula (I) may be prepared from a hydroxyisoquinoline of the formula:—

 --- (II)

by first reacting it with an alkali metal base and then with a halide of the formula:

Q—Y—Z (III)

wherein Y and Z are as defined for formula (I) and Q is Cl, Br or I.

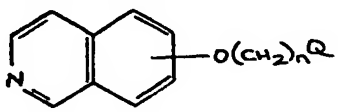
Preferred alkali metal bases are sodium hydride and sodium ethoxide.

In a typical procedure, the hydroxyisoquinoline (II) and the alkali metal base, e.g. sodium ethoxide or sodium hydride, are stirred together, with heating if necessary, for up to about 2 hours. Sodium ethoxide is generally prepared from sodium in ethanol and thus no additional solvent is necessary. In the case of sodium hydride an organic solvent, e.g. dry dimethylformamide, should be present. The halide of the formula (III) is then added, either alone or in a suitable organic solvent such as ethanol or dimethylformamide. The reaction may be allowed to proceed to completion at room temperature but according to the solvent and the reactants it may be advantageous to heat the reaction mixture, e.g. to reflux, to accelerate the reaction. The time taken for the reaction to go substantially to completion will naturally depend on the precise conditions and temperature used and on the nature of the reactants. Ethanol is the preferred solvent when reflux is used. (Dimethylformamide reactions are normally carried out at room temperature). Typically a period of up to about 6 hours at reflux temperature is sufficient. The product may be isolated and purified by conventional procedures.

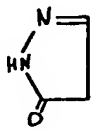
The starting materials of the formulae (II) and (III) are either known compounds or may be prepared by conventional methods.

(2) Compounds of the formula (I) in which —Y—Z is —CH_2CH_2CN or —CH_2CH_2COOH may be prepared by reacting the compound of the formula (II) with, respectively, acrylonitrile or acrylic acid, typically in the presence of a base, e.g. triethylamine or benzyltrimethylammonium hydroxide, and with heating at reflux temperature. The product may be isolated and purified by conventional procedures.

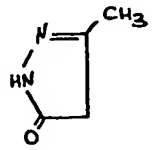
(3) Compounds of the formula (I) in which Y is $(CH_2)_n$ and Z is a 5-oxo-2-pyrazolin-1-yl or 3-methyl-5-oxo-2-pyrazolin-1-yl group may be prepared by reacting a compound of the formula:

 --- (IV)

wherein Q and n are as previously defined, with 2-pyrazolin-5-one:



or 3-methyl-2-pyrazolin-5-one:



in the presence of an alkali metal base, e.g. sodium hydride.

This reaction may typically be carried out by adding the alkali metal base to a solution of the pyrazolinone in a suitable organic solvent, e.g. dry dimethylformamide, and stirring for about an hour at room temperature. The compound (IV), typically in an organic solvent such as dimethylformamide, is then added and the solution heated, e.g. at 80°C for up to about 6 hours. The product may then be isolated and purified by conventional procedure.

(4) Certain of the groups Z may be obtained by chemical transformation reactions and these possibilities will be well known to those skilled in the art.

Thus for example compounds in which Z is —$CONH_2$ may be prepared by the hydrolysis of the corresponding compound in which Z is —CN, using either acid hydrolysis, e.g. with concentrated H_2SO_4, or, in the case of aromatic nitriles, alkaline hydrogen peroxide. They may also be prepared by the reaction of corresponding ester (e.g. the ethyl ester) with liquid ammonia.

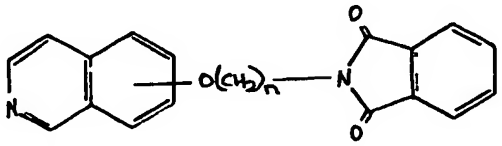
Alkaline hydrolysis of the nitriles or esters in which Z is —$COO(C_1$—C_4 alkyl) can also be used to prepare compounds in which Z is —COOH.

Compounds in which Z is a ureido group —$NHCONHR^5$ may be prepared by reaction with the corresponding compound in which Z is —NH_2 with an alkyl or aryl isocyanate of the formula R^5NCO.

Compounds in which Z is —NHR^4 where R^4 is C_1—C_4 alkylsulphonyl or C_2—C_4 alkanoyl may be prepared by the reaction of the corresponding compound in which Z is —NH_2 with a C_1—C_4 alkylsulphonyl halide or C_2—C_4 alkanoyl halide.

Compounds in which Z is 5-tetrazolyl are prepared from the corresponding cyano derivative by reaction with sodium azide and ammonium chloride.

(5) Compounds in which Y is $(CH_2)_n$ and Z is —NH_2 may be prepared by treating the corresponding phthalimido derivative of the formula:

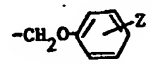


— (V)

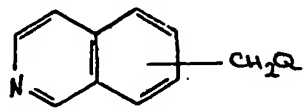
with hydrazine hydrate. Typically the reactants are heated together for a few hours, e.g. under reflux, in a suitable organic solvent, e.g. methanol. The product may then be isolated and purified by conventional procedures.

The starting materials of the formula (V) may be prepared by conventional procedures, e.g. by reaction of the appropriate chloro-alkoxy compound with potassium phthalimide.

(6) Compounds of the formula (I) in which X is

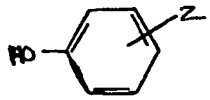


may be prepared by reacting a compound of the formula:—



— (VI)

where Q is as previously defined,
with a compound of the formula:—



(VII)

in the presence of a base such as potassium hydroxide.

Typically the reactants are refluxed together in a suitable solvent, e.g. dry tetrahydrofuran, for up to about 6 hours. The product may be isolated and purified by conventional procedures.

The acid addition salts of the compounds of the formula (I) may also be prepared by conventional procedures.

The compounds of the formula (I) have been found to selectively inhibit the action of the thromboxane synthetase enzyme without significantly inhibiting the action of the prostacyclin synthetase and cyclo-oxygenase enzymes.

Thus the compounds are of value in the treatment of a variety of clinical conditions which are characterised by an inbalance of prostacyclin/thromboxane A_2. For the reasons given below these conditions may include thrombosis, ischaemic heart disease, stroke, transient ischaemic attack, migraine and the vascular complications of diabetes.

Research work has established that in most tissues the major product of the arachidonic acid metabolism in either of two unstable substances, thromboxane A_2 (TxA_2) or prostacyclin (PGI_2). (Proc. Nat. Acad. Sci. U.S.A., 1975, *72*, 2994, Nature, 1976, *263*, 663, Prostaglandins, 1976, *12*, 897). In most cases the prostaglandins PGE_2, PGF_2 and PGD_2 are comparatively minor by-products in this biosynthetic pathway. The discovery of thromboxane A_2 and prostacyclin has significantly increased our understanding of vascular homeostasis, prostacyclin for instance is a powerful vasodilator and inhibitor of platelet aggregation, and in this last respect is the most potent endogenous substance so far discovered. The prostacyclin synthetase enzyme is located in the endothelial layer of the vasculature, and is fed by endoperoxides released by blood platelets coming into contact with the vessel wall. The prostacyclin thus produced is important for prevention of platelet deposition on vessel walls. (Prostaglandins, 1976, *12*, 685, Science, 1976, 17, Nature, 1978, *273*, 765).

Thromboxane A_2 is synthetised by the thromboxane synthetase enzyme which is located in, for example, the blood platelets. Thromboxane A_2 is a powerful vasoconstrictor and pro-aggregatory substance.

As such its actions are in direct opposition to those of prostacyclin. If, for any reason, prostacyclin formation by the vasculature is impaired, then the endoperoxides produced by platelets coming into contact with the vessel wall are converted into thromboxane, but are not converted effectively into prostacyclin (Lancet, 1977, 18, Prostaglandins, 1978, *13*, 3). Alteration of the prostacyclin/thromboxane balance in favour of the latter substance could result in platelet aggregation, vasospasm (Lancet, 1977, 479, Science, 1976, 1135, Amer. J. Cardiology, 1978, *41*, 787) and an increased susceptibility to atherothrombosis (Lancet (i) 1977, 1216). It is also known that in experimental atherosclerosis prostacyclin generation is suppressed and thromboxane A_2 production is enhanced (Prostaglandins, 1977, *14*, 1025 and 1035). Thus thromboxane A_2 has been implicated as the causative agent in variant angina, myocardial infarction, sudden cardiac death and stroke (Thromb. Haemostasis, 1977, 38, 132). Studies in rabbits have shown that ECG changes typical of these conditions were produced when freshly prepared thromboxane A_2 was injected directly into the animal's heart (Biochem. Aspects of Prostaglandins and Thromboxanes, Editors, N. Kharasch and J. Fried, Academic Press 1977 page 189). This technique is considered to represent a unique animal model of the heart attacks of coronary patients and has been used to show that administration of a compound believed to antagonise the effects of thromboxane A_2 protects the rabbits from the adverse consequences of thromboxane A_2 injection.

Another area where a PGI_2/TxA_2 imbalance is considered to be a contributory factor is that of migraine. The migraine headache is associated with changes in intra and extra-cerebral blood flow, in particular a pre-headache reduction of cerebral blood flow followed by dilatation in both vascular areas during the headache phase.

Prior to the development of the headache, blood levels of 5-hydroxytryptamine are elevated, and this suggests the occurrence of *in vivo* aggregation and release of the amine from the platelet stores. It is known that the blood platelets of migraine patients are more prone to aggregate than are those of normal individuals (J. Clin. Pathol., 1971, *24*, 250, J. Headache, 1977, *17*, 101). Furthermore, it has now been postulated that not only is an abnormality of platelet function a major factor in the pathogenesis of migraine attacks but it is in fact their prime cause (Lancet (i), 1978, 501). Thus a drug that selectively modifies platelet function to inhibit thromboxane A_2 formation could be of considerable benefit in migraine therapy.

Abnormalities of platelet behaviour have been reported in patients with diabetes mellitus (Metabolism, 1979, *28*, 394, Lancet, 1978 (i) 235). Diabetic patients are known to be particularly susceptible to microvascular complications, atherosclerosis and thrombosis and platelet hyperreactivity has been suggested as the cause of such angiopathy. Diabetic platelets produce elevated amounts of TxB_2 and malondialdehyde (Symposium "Diabetes and Thrombosis—Implications for Therapy", Leeds U.K., April 1979). Also it has been shown that in rats with experimental diabetes vascular prostacyclin production is impaired and TxA_2 synthesis from the platelets is elevated (IV International Prostaglandin Conference, Washington, D.C. May 1979).

Thus the imbalance between prostacyclin and TxA_2 is considered to be responsible for the

microvascular complications of diabetes. A TxA_2- synthetase inhibitor could therefore find clinical utility in preventing these vascular complications.

Aspirin and most other non-steroidal anti-inflammatory drugs inhibit the cyclo-oxygenase enzyme. The effect of this is to shut down the production of the PGG_2/H_2 endoperoxides and by so doing to reduce both the prostacyclin and thromboxane A_2 levels. Aspirin and aspirin-like drugs have been evaluated clinically for prevention of stroke and heart attack (New England and J. Med. 1978, *299*, 53, B.M.J. 1978, 1188, Stroke, 1977, *8* 301).

Although some encouraging results have been obtained with these drugs, a compound which specifically inhibits thromboxane A_2 formation leaving the biosynthesis of prostacyclin unimpaired would be more valuable in these clinical conditions (Lancet (ii), 1978, 780).

The effect of the compounds of the formula (I) on the thromboxane synthetase enzyme, and the prostacyclin synthetase and cyclo-oxygenase enzymes has been measured by the following *in vitro* enzyme assays:—

1. Cyclo-oxygenase

Ram seminal vesicle microsomes (Biochemistry, 1971, *10*, 2372) are incubated with arachidonic acid (100 μM: 1 min.: 22°) to produce PGH_2 and aliquots of the reaction mixture injected into a stream of Krebs-bicarbonate at 37°C (containing a mixture of antagonists (Nature, 1978, *218*, 1135) and indomethacin (Brit. J. Pharmacol., 1972, *45*, 451) which is superfusing a spirally-cut rabbit aorta strip (Nature 1969, *223*, 29). The ability of a compound to inhibit the enzyme is measured by comparing the increases in isometric tension produced by PGH_2 in the absence of the test compound, and following pre-incubation of the enzyme with the test compound for 5 minutes.

2. Prostacyclin (PGI_2) Synthetase

Pig aorta microsomes (Nature, 1976, *263*, 663) are incubated (30 sec.: 22°C) with PGH_2 produced as in 1) and aliquots bio-assayed as in 1. PGI_2 production is assessed indirectly by measuring the decrease in PGH_2-induced tension (PGI_2 itself does not contract the aorta). This decreased can be prevented completely by pre-incubation of the enzyme with the selective PGI_2 synthetase inhibitor, 15-hydroperoxy-arachidonic acid (Prostaglandins, 1976, *12*, 715). The test compound is then pre-incubated with the enzyme for 5 minutes, and its ability to prevent the decreased in tension is measured.

3. Thromboxane A_2 (TxA_2) Synthetase

Indomethacin pre-treated human platelet microsomes (Science 1976, *193* 163) are incubated (2 min.: 0°C) with PGH_2 (produced as in 1) and aliquots of the reaction mixture superfused over two rabbit aorta spirals which are separated by a delay coil (2 min.). The latter is required to allow the selective decay of the more unstable thromboxane A_2 (Proc. Nat. Acad. Sci., 1975, *72*, 2994) thereby enabling the separate measurement of increased isometric tension due to the TxA_2 formed and the PGH_2 remaining. The test compound is pre-incubated with the enzyme for 5 minutes, and its ability to inhibit the thromboxane synthetase enzyme is measured as its reduction of the TxA_2 component of the isometric tension.

Compounds of the invention tested in this way have been shown to be capable of selectively inhibiting the thromboxane synthetase enzyme.

In addition to the above, an *in vitro* assay for measuring the inhibition of human blood platelet aggregation has been described and this may be predictive of anti-thrombotic efficacy clinically (Lancet (ii), 1974,, 1223, J. Exp. Med., 1967, *126*, 171). Both clinically effective agents aspirin and sulphinpyrazone show inhibitory activity *in vitro* against a variety of aggregating agents in this test.

A number of *in vivo* tests in animals have also been described for evaluating potential anti-thrombiotic drugs.

Intravenous injection of arachidonic acid causes death in rabbits by causing platelet clumping and embolisation in the lungs. Again both the clinically effective aspirin (Agents and Actions, 1977, 1, 481) and sulphinpyrazone (Pharmacology, 1976, *14*, 522) protect the rabbit from the lethal effect of the injection. Sulphinpyrazone has also been shown to prevent the aggregation of platelets in an extra corporeal loop of the abdominal aorta of rats *in vivo* (Thromb. Diathes. Haem., 1973, *30*, 138).

The compounds may be administered orally in the form of tablets or capsules containing a unit dose of the compound together with such excipients as maize starchm calcium carbonate, dicalcium phosphate, alginic acid, lactose, magnesium stearate, "Primogel" (Trade Mark) or talc. The tablets are typically prepared by granulating the ingredients together and compressing the resulting mixture to give tablets of the desired size. Capsules are typically prepared by granulating the ingredients together and filling them into hard gelatine capsules of the appropriate size to contain the desired dosage.

The compounds may also be administered parenterally, for example by intramuscular, intravenous or subcutaneous injection. For parenteral administration, they are best used in the form of a sterile aqueous solution which may contain other solutes such as tonic and pH adjusters. The compounds may be added to distilled water and the pH adjusted to 3—6 using an acid such as citric, lactic or hydrochloric acid. Sufficient solutes such as dextrose or saline may be added to render the

solution isotonic. The resulting solution may then be sterilised and filled into sterile glass vials of an appropriate size to contain the desired volume of solution.

The compounds of the invention may also be administered by the infusion of a parenteral formulation as described above into a vein.

For oral administration to human patients, it is expected that the daily dosage level of a compound of the invention will be from 0.1 to 20 mg/kg per day for a typical adult patient (70 kg). For parenteral administration, it is expected that the daily dosage level of a compound of the formula (I) will be from 0.01—0.5 mg/kg per day, for a typical adult patient. Thus tablets or capsules can generally be expected to contain from 5 to 150 mg of the active compound for administration orally up to 3 times a day. Dosage units for parenteral administration can be expected to contain from 0.5—35 mg of the active compound. A typical vial could be a 10 ml vial containing 5 mg of the active compound in 6—10 ml of solution.

It should of course be appreciated that the physician in any event will determine the actual dosage which will be most suitable for the individual and it will vary with the age, weight and response of the patient. The above dosages are exemplary of the average patient, there may of course be individual cases where higher or lower dosage ranges are merited.

The preparation of the novel compounds of the invention is illustrated by the following Examples:—

Example 1

Preparation of 3-(5-Isoquinolyloxy)propionitrile

5-Hydroxyisoquinoline (10 g), acrylonitrile (25 g) and benzyltrimethylammonium hydroxide (40% in 2.5 ml methanol) were stirred for 16 hours in ethanol (30 ml) at reflux temperature. The solution was then concentrated under reduced pressure and the residue partitioned between ethyl acetate and 2N sodium hydroxide. The organic layer was separated, washed with water and dried over sodium sulphate, filtered and evaporated to give an oil which crystallised on standing. Recrystallisation from ethyl acetate afforded the title compound, 1.0 gm, m.p. 102—104°C.

Analysis %:—

Found:	C, 72.4, H, 5.0, N, 14.5.
Calculated for $C_{12}H_{10}N_2O$:	C, 72.7, H, 5.1, N, 14.1.

Example 2

Preparation of 3-(5-Isoquinolyloxy)propionamide

3-(5-Isoquinolyloxy)propionitrile (0.9 g) was added portionwise with stirring to 85% sulphuric acid (15 ml) at a temperature of between 10—15°C. The solution was then stirred at room temperature for 3 hours before pouring onto crushed ice with basifying to pH 10 with 2N sodium hydroxide solution. The resultant solid amide (the title compound) was then filtered, washed, and recrystallised from methanol/water, yield 0.25 g, m.p. 176—178°C.

Analysis %:—

Found:	C, 66.3, H, 5.6, N, 12.8.
Calculated for $C_{12}H_{12}N_2O_2$:	C, 66.6, H, 5.6, N, 13.0.

Example 3

Preparation of 3-(5-Isoquinolyloxy)propionic Acid 3/4 Hydrate

5-Hydroxyisoquinoline (1.0 g), acrylic acid (1.0 ml) and triethylamine (10 ml) were heated on a steam bath for 3½ hours. At the end of this time a brown solid was observed which was filtered, washed with 40—60° petroleum ether, and recrystallised from water to give the title compound, yield 0.8 g, m.p. 217—221°C.

Analysis %:—

Found:	C, 62.3, H, 5.0, N, 6.2.
Calculated for $C_{12}H_{11}NO_3.3/4H_2O$:	C, 62.5, H, 5.5, N, 6.1.

Example 4

Preparation of:

(A) Ethyl (5-Isoquinolyloxy)acetate Hydrochloride and

(B) (5-Isoquinolyloxy)acetic Acid

A. 5-Hydroxyisoquinoline (7.25 g) was added at room temperature to a stirred solution of sodium 1.2 g) in ethanol (100 ml).

The solution was then heated to reflux temperature before the dropwise addition of ethyl bromoacetate (8.35 g), whereupon heating was continued for a further 4 hours. The solution was then concentrated under reduced pressure and the residue partitioned between water and ether, the layers separated and the aqueous layer extracted with ether (3x100 ml). The combined organic extracts were

washed, dried (Na_2SO_4) and evaporated to give ethyl (5-isoquinolyloxy) acetate as an oil, yield 4.3 g. A portion of this oil was converted to the hydrochloride salt, m.p. 183—185°C, using ethereal hydrogen chloride and recrystallising from isopropanol.

Analysis %:—

Found:	C, 57.9,	H, 5.2,	N, 5.6.
Calculated for $C_{13}H_{13}NO_3HCl$:	C, 58.3,	H, 5.3,	N, 5.2.

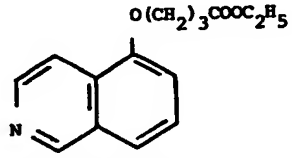
B. The remaining ester (3.5 g) (free base) was added to a solution of sodium hydroxide (3.5 g) in water (70 ml) and ethanol (20 ml) and warmed on a steam bath for 3 hours. Ethanol was removed by evaporation under reduced pressure and the aqueous residue washed and acidified to pH 4.0 with concentrated hydrochloric acid. A solid precipitated from the solution and was filtered, washed and recrystallised from methanol to give (5-isoquinolyloxy)acetic acid, yield 1.5 g, m.p. 214—216°C.

Analysis %:—

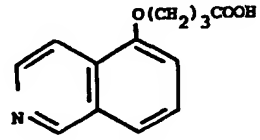
Found:	C, 64.8,	H, 4.6,	N, 6.8.
Calculated for $C_{11}H_9NO_3$:	C, 65.0,	H, 4.5,	N, 6.9.

Example 5

By the procedure of Example 4 Parts A and B respectively, the following compounds were prepared, starting from 5-hydroxyisoquinoline and ethyl 4-bromo-*n*-butyrate:



This was not characterised and was used directly in the next stage.



m.p. 177—178°C.

Analysis %:—

Found:	C, 67.2,	H, 5.7,	N, 6.2.
Calculated for $C_{13}H_{13}NO_3$:	C, 67.5,	H, 5.7,	N, 6.0.

Example 6

(A) Preparation of 2-(5-Isoquinolyloxy)ethyl Chloride

5-Hydroxyisoquinoline (17.4 g) was dissolved in dry dimethylformamide (200 ml) and sodium hydride (7.8 g) added portionwise with stirring under dry nitrogen. After 2 hours a solution of 2-(benzenesulphonyloxy)ethyl chloride (29.1 g) in dry dimethylformamide (50 ml) was added dropwise and the mixture stirred at room temperature overnight. After evaporation of dimethylformamide a 10% aqueous sodium hydroxide solution (25 ml) was added to the residue and the mixture extracted with ether (3x100 ml). The combined ether extracts were washed, dried, filtered and evaporated to give a solid which crystallised after trituration with 60/80° petroleum ether to the title compound, used directly in the next stage.

(B) Preparation of N-(2-[5-Isoquinolyloxy]ethyl)phthalimide

2-(5-Isoquinolyloxy)ethyl chloride (10.0 g) was added to dry dimethylformamide (100 ml) containing potassium phthalimide (8.91 g) and the mixture heated on the steam bath for 18 hours. After evaporation to dryness water (100 ml) was added to the residue and the mixture extracted with ether (4x75 ml). The combined organic extracts were washed, dried, filtered and evaporated to give a yellow solid which was recrystallised from ethanol to give the title compound, 12.1 g, m.p. 181—183°C.

Analysis %:—

Found:	C, 71.1,	H, 4.6,	N, 8.7.
Calculated for $C_{19}H_{14}N_2O_3$:	C, 71.7,	H, 4.4,	N, 8.8.

(C) Preparation of 2-(5-Isoquinolyloxy)ethylamine Dihydrochloride

The phthalimide derivative prepared in (B) (12.0 g) was added to methanol (75 ml) containing hydrazine hydrate (2.0 g) and the mixture heated at reflux on a steam bath for 3 hours. After cooling the mixture was evaporated to dryness, stirred with chloroform (50 ml) and filtered. The filtrate was evaporated to give an oil from which more solid material was obtained after trituration with ether. The solid was again filtered off and the filtrate evaporated to give an oil, 4.25 g.

A portion of this oil was added to ethereal hydrogen chloride and the resultant solid filtered, washed and recrystallised from ethanol to give the title compound, m.p.>250°C.

Analysis %:—

Found:	C, 50.4,	H, 5.3,	N, 10.6.
Calculated for $C_{11}H_{12}N_2O.2HCl$:	C, 50.6,	H, 5.4,	N, 10.7.

Example 7

Preparation of 1-(2-[5-Isoquinolyloxy]ethyl)-3-methylurea

2-(5-Isoquinolyloxy)ethylamine (0.83 g) was dissolved in dry dichloromethane (10 ml) and added dropwise to a solution of methylisocyanate (0.28 g) in dichloromethane (15 ml). The mixture was stirred at room temperature for 2 hours before evaporation to dryness. The resultant yellow solid was crystallised from ethyl acetate to give the title compound, yield 0.4 g, m.p. 156—158°C.

Analysis %:—

Found:	C, 63.5,	H, 6.2,	N, 16.7.
Calculated for $C_{13}H_{15}N_3O_2$:	C, 63.7,	H, 6.2,	N, 17.1.

Example 8

By a similar procedure to that of Example 7, 1-(2-[5-isoquinolyloxy]ethyl)-3-phenylurea, m.p. 176°C, was prepared from 2-(5-isoquinolyloxy)ethylamine and phenylisocyanate.

Analysis %:—

Found:	C, 70.0,	H, 5.7,	N, 13.3.
Calculated for $C_{18}H_{17}N_3O_2$'	C, 70.3,	H, 5.6,	N, 13.7.

Example 9

Preparation of 5-(p-Cyanobenzyloxy)isoquinoline

Sodium hydride (1.5 g) was added to a solution of 5-hydroxy-isoquinoline (4.0 g) in dry dimethylformamide (DMF) (100 ml) and the mixture stirred at room temperature for 1 hour under dry nitrogen. α-Bromo-4-toluonitrile (5.4 g) in dry dimethylformamide (100 ml) was then added dropwise and the stirring continued overnight at room temperature. After evaporation of the volatile components, water (100 ml) was added and the mixture extracted with chloroform (4x100 ml), the organic extracts were combined, washed, dried, filtered and evaporated to give a solid which was recrystallised from water/ethanol to give the title compound, 4.0 g, m.p. 150—153°C.

Analysis %:—

Found:	C, 78.9,	H, 4.8,	N, 10.8.
Calculated for $C_{17}H_{12}N_2O$:	C, 78.4,	H,4.7,	N, 10.8.

Example 10

Preparation of 5-(p-carbamoylbenzyloxy)isoquinoline

The nitrile prepared in Example 9 (2.0 g) was suspended in ethanol (10 ml) and sodium hydroxide (2.4 g in 10 ml H_2O) was then added followed by 100 vol. hydrogen peroxide (10 ml). The mixture was stirred at room temperature for 4 hours before being poured onto ice/water. The resultant precipitate was filtered off and recrystallised from methanol to give the title compound, yield 1.2 g, m.p. 209—217°C.

Analysis %:—

Found:	C, 73.1,	H, 5.2,	N, 9.7.
Calculated for $C_{17}H_{14}N_2O_2$:	C, 73.4,	H, 5.1,	N, 10.1.

Example 11

Preparation of 5-(p-carboxybenzyloxy)isoquinoline

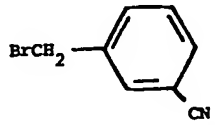
The nitrile prepared in Example 9 (1.9 g) was suspended in 10% potassium hydroxide solution (25 ml) and heated at reflux for 18 hours. The cooled solution was then poured into water (50 ml) and acidified with glacial acetic acid (10 ml). The resultant precipitate was filtered, dried and recrystallised from water/dimethylformamide to give the title compound: 1.5 g, m.p. 234—245°C.

Analysis %:—

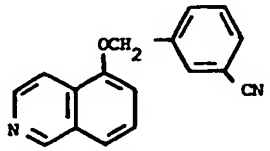
Found:	C, 72.5,	H, 4.7,	N, 4.8.
Calculated for $C_{17}H_{13}NO_3$:	C, 73.1,	H, 4.7,	N, 5.0.

Example 12

By a procedure similar to that of Example 9, using sodium hydride, 5-hydroxyisoquinoline and:



the following compound was prepared:



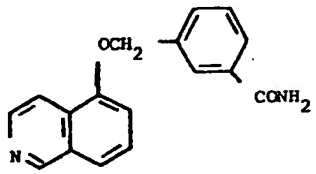
m.p. 106—108°C.

Analysis %:—

Found:	C, 78.2,	H, 4.7,	N, 10.7.
Calculated for $C_{17}H_{12}N_2O$:	C, 78.4,	H, 4.6,	N, 10.8.

Example 13

By a procedure similar to that of Example 10, the following compound was prepared by the hydrolysis of the product of Example 12:



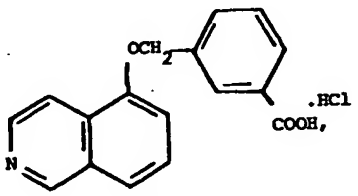
m.p. 165—169°C.

Analysis %:—

Found:	C, 73.4,	H, 5.0,	N, 9.8.
Calculated for $C_{17}H_{14}N_2O_2$:	C, 73.4,	H, 5.1,	N, 10.1.

Example 14

By a procedure similar to that of Example 11, the following compound was prepared by the hydrolysis of the product of Example 12 and characterised as the hydrochloride:



m.p. 243—247°C.

Analysis %:—

Found:	C, 63.8,	H, 4.5,	N, 4.7.
Calculated for $C_{17}H_{13}NO_3.HCl$:	C, 64.7,	H, 4.5,	N, 4.4.

Example 15

Preparation of 5-(2-[Methanesulphonamido]ethoxy)isoquinoline

5-(2-Aminoethoxy)isoquinoline (0.63 g) was dissolved in dry methylene chloride (10 ml) and to this was added triethylamine (2.0 ml) and the solution cooled to 0°C. Mesyl chloride (0.4 g) in dry methylene chloride (10 ml) was then added dropwise and the mixture stirred at room temperature for 2 hours. The solvent was then removed under reduced pressure, water (25 ml) added to the residue and

the mixture extracted with chloroform (3x25 ml). The combined organic extracts were washed, dried, filtered and evaporated to give a solid which was recrystallised from toluene to give the title compound, yield 0.3 g, m.p. 158—162°C.

Analysis %:—
Found: C, 54.0, H, 5.7, N, 10.2.
Calculated for $C_{12}H_{14}N_2O_3S$: C, 54.1, H, 5.3, N, 10.5.

Example 16

By a procedure similar to that of Example 4 (A), 5-(3-cyano-*n*-propoxy)isoquinoline, m.p. 71—73°C, was prepared from 5-hydroxy-isoquinoline, sodium in ethanol (sodium ethoxide) and 4-bromo-*n*-butyronitrile.

Analysis %:—
Found: C, 73.9, H, 5.7, N, 13.2.
Calculated for $C_{13}H_{12}N_{20}$: C, 73.6, H, 5.7, N, 13.2.

Example 17

Preparation of 5-[3-(5-Tetrazolyl)-n-propoxy]isoquinoline Hemihydrate

5-[3-Cyano-*n*-propoxy]isoquinoline (2.12 g) was dissolved in dry dimethylformamide (25 ml) and to this was added sodium azide (3.25 g) and ammonium chloride (2.67 g). The mixture was heated at 120°C for 4 days, the solvent then removed under reduced pressure and 8% sodium bicarbonate solution (200 ml) added. The solution was filtered, acidified to pH 4 with concentrated hydrochloric acid, filtered, and the solid washed with water and recrystallised from methanol with charcoaling to give the title compound, yield 0.68 g, m.p. 212—216°C.

Analysis %:—
Found: C, 59.0, H, 5.2, N, 26.6.
Calculated for $C_{13}H_{13}N_5O:\frac{1}{2}H_2O$: C, 59.1, H, 5.3, N, 26.5.

Example 18

Preparation of 5-[3-Carbamoyl-*n*-propoxy]isoquinoline

5-[3-Cyano-*n*-propoxy]isoquinoline (9.0 g) was added in portion with stirring to 85% sulphuric acid (100 ml) at a temperature of 10—15°C. A clear solution was obtained after 20 minutes and stirring was continued at room temperature for 3 hours. The solution was then cautiously poured into ice water, basified with solid sodium hydroxide pellets to pH 8 and the resultant yellow solid filtered and washed with water. Recrystallisation from methanol afforded the title compound: 2.25 g, m.p. 185—187°C.

Analysis %:—
Found: C, 67.8, H, 6.1, N, 11.8.
Calculated for $C_{13}H_{14}N_2O_2$: C, 67.8, H, 6.1, N, 12.2.

Example 19

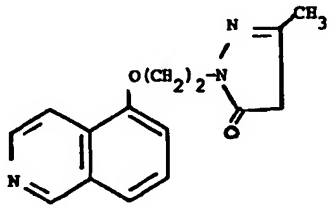
Preparation of 1-(2-[5-isoquinolyloxy]ethyl)-3-methyl-2-pyrazolin-5-one

Sodium hydride (0.86 g) was added in portions to a stirred solution of 3-methyl-2-pyrazolin-5-one (1.6 g) in dry dimethylformamide (50 ml) and the mixture stirred for 1 hour at room temperature under a nitrogen atmosphere. 5-(2-Chloro ethoxy) isoquinoline (1.7 g) in dry dimethylformamide (50 ml) was then added dropwise to the solution which was then heated to 120°C and kept briefly at this temperature before cooling to 80°C.

The temperature was maintained at 80°C for a period of 6 hours, then the reaction mixture was cooled and left to stand overnight at room temperature. The solvents were removed under reduced pressure and water (100 ml) was added to the residue which was then extracted with chloroform (3x50 ml). The combined organic extracts were washed, dried, filtered and evaporated to give an oil which crystallised after trituration with diethyl ether. Recrystallisation from ethyl acetate yielded 0.3 gms of the title compound, m.p. 149—151°C.

Analysis %:—
Found: C, 67.4, H, 5.7, N, 15.5.
Calculated for $C_{15}H_{14}N_3O_2$: C, 66.9, H, 5.6, N, 15.6.

The product had the formula:



Example 20

Preparation of 2-Ethoxycarbonyl-5-[5-isoquinolyloxymethyl]thiophene

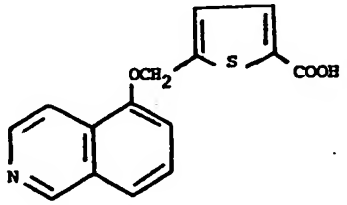
5-Hydroxyisoquinoline (2.9 g) was dissolved in dry dimethylformamide (50 ml) and the solution stirred under a nitrogen atmosphere at room temperature. Sodium hydride (1.06 g) was added in portions and the stirring continued for 1.5 hours. A solution of 5-bromomethyl-2-ethoxycarbonylthiophene (4.98 g) in dry dimethylformamide (25 ml) was added dropwise and the mixture stirred at room temperature overnight. The solvent was then removed under reduced pressure and a 10% aqueous sodium hydroxide solution added to the residue. The mixture was extracted with methylene chloride (3x50 ml) and the combined extracts washed, dried (Na_2SO_4), filtered and evaporated to give an oil. After chromatography and recrystallisation from 80—100° petrol/ether, the title compound was obtained, yield 1.9 g, m.p. 91°C.

Analysis %:—

Found:	C, 65.4, H, 5.1, N, 3.9.
Calculated for $C_{17}H_{15}NO_3S$:	C, 65.2, H, 4.8, N, 4.45.

Example 21

By a procedure similar to that of Example 11, the following compound was prepared by the hydrolysis of the product of Example 20:



m.p. 224—227°C.

Analysis %:—

Found:	C, 62.75, H, 3.9, N, 5.15.
Calculated for $C_{15}H_{11}NO_3S$:	C, 63.1, H, 3.9, N, 4.9.

Example 22

Preparation of 2-Carbamoyl-5-(5-isoquinolyloxymethyl)thiophene

The product of Example 20 (0.7 g) was charged to a 125 ml Parr bomb, cooled to —40°C and liquid ammonia (25 ml) was added. The bomb was then sealed and heated with stirring to 100°C for 18 hours. After cooling to room temperature the bomb was opened and the excess ammonia allowed to evaporate. The residual solid was recrystallised from isopropylalcohol to give the title compound, yield 0.2 g, m.p. 213—215°C.

Analysis %:—

Found:	C, 63.1, H, 4.3, N, 9.45.
Calculated for $C_{15}H_{12}N_2O_2S$:	C, 63.35, H, 4.3 N, 9.85.

Example 23

7-(4-Cyanobenzyloxy)isoquinoline

Treatment of 7-hydroxyisoquinoline (2.90 g) in dry dimethylformamide (50 ml) with sodium hydride (1.0 g of 50% dispersion) followed by α-bromo-4-toluonitrile I(4.0 g) by the method of Example 9 gave 7-(4-cyanobenzyloxy)isoquinoline (3.58 g), m.p. 142—144°C (from ethyl acetate).

Analysis %:—

Found:	C, 77.93 H, 4.70, N, 10.56.
Calculated for $C_{17}H_{12}N_2O$:	C, 78.44, H, 4.65, N, 10.76.

Example 24
7-(4-Carbamoylbenzyloxy)isoquinoline

Treatment of 7-(4-cyanobenzyloxy)isoquinoline (1.80 g) with 6N sodium hydroxide (9.0 ml) and 30% hydrogen peroxide (9.0 ml) in ethanol (40 ml) by the method of Example 10 gave 7-(4-carbamoylbenzyloxy)isoquinoline (0.90 g), m.p. 237—239°C (from methanol).

Analysis %:—

Found:	C, 73.53,	H, 5.08,	N, 10.28.
Calculated for $C_{17}H_{14}N_2O_2$:	C, 73.36,	H, 5.07,	N, 10.07.

Example 25
7-(4-Carboxybenzyloxy)isoquinoline Hydrochloride

Hydrolysis of 7-(4-cyanobenzyloxy)isoquinoline by the method of Example 11 gave a solid which was dissolved in 5N HCl. Evaporation of the solution gave a solid which was crystallized from acetic acid to give 7-(4-carboxybenzyloxy)isoquinoline hydrochloride, m.p. 248—250°C.

Analysis %:—

Found:	C, 64.20,	H, 4.45,	N, 4.20.
Calculated for $C_{17}H_{13}NO_3HCl$:	C, 64.66,	H, 4.47,	N, 4.44.

Example 26
Ethyl (7-isoquinolyloxy)acetate Hydrochloride

Successive treatment of 7-hydroxyisoquinoline (2.90 g) in dry dimethylformamide (50 ml) and sodium hydride (1.0 g of 50% dispersion) followed by ethyl bromoacetate (3.60 g) by the method of Example 9 gave an oil which was chromatographed on silica gel. Elution with chloroform gave first some impurity and mineral oil followed by pure product. The product containing fractions were combined to give an oil. A portion of the oil was dissolved in ether and treated with an excess of ethereal HCl solution to give a solid. The solid was filtered off and crystallized from isopropanol to give ethyl (7-isoquinolyloxy)acetate hydrochloride, m.p. 188—189°C.

Analysis %:—

Found:	C, 58.38,	H, 5.37,	N, 5.52.
Calculated for $C_{13}H_{13}NO_3.HCl$:	C, 58.32,	H, 5.27,	N, 5.23.

Example 27
(7-isoquinolyoxy)acetamide

Ethyl (7-isoquinolyloxy)acetate (2.0 g) was suspended in concentrated aqueous ammonia solution (10 ml) and just sufficient ethanol was added to achieve complete solution. The solution was allowed to stand for 2 hours and the resulting solid was filtered off and crystallized from water to give (7-isoquinolyloxy) acetamide (0.91 g), m.p. 181—182°C.

Analysis %:—

Found:	C, 65.54,	H, 5.03,	N, 13.77.
Calculated for $C_{11}H_{10}N_2O_2$:	C, 65.33,	H, 4.98,	N, 13.86.

Example 28
(7-Isoquinolyloxy)acetic Acid Hydrochloride

A mixture of ethyl (7-isoquinolyloxy)acetate (2.60 g) and concentrated hydrochloric acid was heated on a steam bath for 3.5 hours and the resulting solution was evaporated. The residue was crystallized from 5N HCl to give (7-isoquinolyloxy)acetic acid hydrochloride (1.50 g), m.p. 232—233°C.

Analysis %:—

Found:	C, 55.15,	H, 4.18,	N, 5.96.
Calculated for $C_{11}H_9NO_3.HCl$:	C, 55.13,	H, 4.21,	N, 5.85.

Example 29
7-(4-Cyanophenoxy)isoquinoline

7-Hydroxyisoquinoline (2.90 g) was dissolved in dry dimethylsulphoxide (50 ml) and sodium hydride (1.0 g of 50% dispersion) was added portionwise with stirring. The mixture was stirred at room temperature for 1.5 hours and then 4-nitrobenzonitrile (3.0 g) was added. The resulting mixture was allowed to stand at room temperature for 48 hours, then heated at 100°C for 2 hours and finally cooled and poured onto ice. The mixture was extracted several times with ethyl acetate and the combined extracts were washed well with water and dried (Na_2SO_4). The solvent was evaporated and the residue was chromatographed on silica gel. Elution with chloroform gave a solid which was further

purified by dissolving in a small volume of chloroform and addition of a large excess of ethereal HCl to the solution. The resulting product hydrochloride was filtered off and dissolved in water. The solution was filtered and the filtrate was treated with aqueous sodium bicarbonate solution until alkaline. The solid was filtered off, washed with water and dried to give 7-(4-cyanophenoxy)isoquinoline (2.77 g), m.p. 136—137°C.

Analysis %:—

Found:	C, 77.97,	H, 4.09,	N, 11.36.
Calculated for $C_{16}H_{10}N_2O$:	C, 78.03,	H, 4.09,	N, 11.38.

Example 30

7-(4-Carbamoylphenoxy)isoquinoline

Treatment of 7-(4-cyanophenoxy)isoquinoline (1.20 g) with 6N sodium hydroxide (6.0 ml) and 30% hydrogen peroxide (6.0 ml) in ethanol (30 ml) by the method of Example 10 gave 7-(4-carbamoylphenoxy) isoquinoline (0.94 g), m.p. 198—199°C (from ethanol).

Analysis %:—

Found:	C, 72.56,	H, 4.61,	N, 10.56.
Calculated for $C_{16}H_{12}N_2O_2$:	C, 72.71,	H, 4.58,	N, 10.60.

Example 31

7-(4-Carboxyphenoxy)isoquinoline

Hydrolysis of 7-(4-cyanophenoxy)isoquinoline by the method of Example 11 gave a solid which was crystallized from acetic acid to give 7-(4-carboxyphenoxy)isoquinoline, m.p. 277—279°C.

Analysis %:—

Found:	C, 72.18,	H, 4.23,	N, 5.10.
Calculated for $C_{16}H_{11}NO_3$:	C, 72.44,	H, 4.18,	N, 5.28.

Example 32

Ethyl 4-(7-Isoquinolyloxy)butyrate Hydrochloride

7-Hydroxyisoquinoline (5.80 g) was dissolved in dry dimethylformamide (50 ml) and sodium hydride (2.0 g of 50% dispersion) was added portionwise with stirring. The mixture was stirred at room temperature for 1 hour and then ethyl 4-bromobutyrate (8.0 g) was added dropwise over 5 minutes. The mixture was then stirred at room temperature for 20 hours and then heated at 100°C for 3 hours. It was then evaporated and the residue was partitioned between chloroform and water. The chloroform layer was washed well with water and dried (Na_2SO_4). Evaporation of the solvent gave an oil which was chromatographed on silica gel. Elution with chloroform first gave mineral oil and some impurity followed by pure product. Evaporation of the product containing fractions gave an oil (5.75 g). A portion of the oil was dissolved in a small volume of ether and treated with an excess of ethereal HCl solution. The solid was filtered off and crystallized from isopropanol to give ethyl 4-(7-isoquinolyloxy)butyrate hydrochloride, m.p. 191—193°C.

Analysis %:—

Found:	C, 60.66,	H, 5.97,	N, 4.65.
Calculated for $C_{15}H_{17}NO_3$·HCl:	C, 60.91,	H, 6.13,	N, 4.74.

Example 33

4-(7-Isoquinolyloxy)butyramide

A mixture of ethyl 4-(7-isoquinolyloxy)butyrate (2.0 g) and concentrated aqueous ammonia solution (SG 0.88) (20 ml) was heated for 3 hours at 150°C in a bomb. The mixture was cooled and evaporated to give an oil which was chromatographed on silica gel. Elution with chloroform removed a small amount of starting material and elution with a mixture of chloroform and methanol (9:1) gave the product as an oily solid. Further purification was carried out by dissolving the solid in a small volume of dilute HCl, filtering the solution and making the filtrate just alkaline with sodium bicarbonate solution. The solid was filtered off, washed with water, dried and crystallized from ethyl acetate/petrol to give 4-(7-isoquinolyloxy)butyramide (0.30 g), m.p. 162—164°C.

Analysis %:—

Found:	C, 68.08,	H, 6.18,	N, 12.05
Calculated for $C_{13}H_{14}N_2O_2$	C, 67.81,	H, 6.13,	N, 12.17.

Example 34

4-(7-Isoquinolyloxy)butyric Acid Hydrochloride

Hydrolysis of 4-(7-isoquinolyloxy)butyrate (2.0 g) with concentrated hydrochloric acid (15 ml) by the method of Example 28 gave 4-(7-isoquinolyloxy)butyric acid hydrochloride (0.60 g), m.p. 213—215°C (from acetic acid/ethyl acetate).

Analysis %:—

Found:	C, 57.79,	H, 5.18,	N, 4.81.
Calculated for $C_{13}H_{13}NO_3.HCl$:	C, 58.32,	H, 5.27,	N, 5.23%.

Example 35

5-[(5-Carbethoxypyrid-2-yl)methoxy]isoquinoline

Treatment of 5-hydroxyisoquinoline in dry dimethylformamide with sodium hydride (50% dispersion) followed by ethyl 6-chloromethylnicotinate by the method of Example 9 gave 5-[(5-carbethoxypyrid-2-yl)methoxy]isoquinoline, m.p. 117—118°C (from cyclohexane).

Analysis %:—

Found:	C, 70.09,	H, 5.22,	N, 8.97.
Calculated for $C_{18}H_{16}N_2O_3$:	C, 70.11,	H, 5.23,	N, 9.09.

Example 36

5-[4-(2-Pyridylcarbamoyl)benzyloxy]isoquinoline

Carbonyldi-imidazole (0.89 g) was added to a solution of 5-(4-carboxybenzyloxy)isoquinoline (1.50 g) in dry tetrahydrofuran (25 ml) and dry dimethylformamide (50 ml) and the solution was stirred at room temperature for 2 hours. 2-Aminopyridine (0.53 g) was then added and the resulting solution was stirred for 18 hours and then evaporated to dryness. The residue was partitioned between 5% sodium bicarbonate solution (ca. 100 ml) and chloroform and the organic layer was separated. The aqueous layer was extracted with chloroform and the combined organic layer and extracts were dried ($MgSO_4$) and evaporated to give a solid which was chromatographed on silica gel. Elution with methylene chloride/methanol (50:1) gave first some impurity followed by pure product. The product-containing fractions were combined and evaporated to give a solid which was crystallized from toluene to give 5-[4-(2-pyridylcarbamoyl)benzyloxy]isoquinoline (0.11 g), m.p. 208—209°C.

Analysis %:—

Found:	C, 73.66,	H, 5.01,	N, 11.92.
Calculated for $C_{22}H_{17}N_3O_2$:	C, 74.35,	H, 4.82,	N, 11.82

Example 37

A. 5-(3-Phthalimidopropoxy)isoquinoline

Treatment of 5-hydroxyisoquinoline in dry dimethylformamide with sodium hydride (50% dispersion) followed by N-(3-bromopropyl)phthalimide by the method of Example 9 gave 5-(3-phthalimido-propoxy)isoquinoline, m.p. 193—194°C (from methanol).

Analysis %:—

Found:	C, 71.95,	H, 4.95,	N, 8.40.
Calculated for $C_{20}H_{16}N_2O_3$:	C, 72.27,	H, 4.85,	N, 8.43.

B. N-[3-(5-Isoquinolyloxy)propyl]-N¹-methylurea

A mixture of 5-(3-phthalimidopropoxy)isoquinoline (12.0 g) and hydrazine hydrate (2.0 g) in methanol (75 ml) was heated under reflux for 4 hours and then cooled. The mixture was filtered and the filtrate was evaporated to dryness. The residue was suspended in chloroform (75 ml) and the mixture was filtered. The filtrate was evaporated to dryness to give 5-(3-aminopropoxy)isoquinoline (9.5 g) as an oil which was used without further purification.

The above amine (1.06 g) in dry methylene chloride (10 ml) was added dropwise to a stirred solution of methyl isocyanate (0.31 g) in dry methylene chloride (15 ml). The solution was stirred at room temperature for 1.5 hours, and then evaporated to dryness. The residue was crystallized from chloroform/petrol to give N-[3-(5-isoquinolyloxy)propyl]-N¹-methylurea (0.90 g), m.p. 115—117°C.

Analysis %:—

Found:	C, 64.48,	H, 6.76,	N, 16.18.
Calculated for $C_{14}H_{17}N_3O_2$:	C, 64.84,	H, 6.61,	N, 16.21.

Example 38

5-(4-Carbethoxyphenoxymethyl)isoquinoline

A solution of *n*-butyllithium in hexane (12.0 ml of 1.6 M solution) was added dropwise with stirring to a solution of 5-brom-isoquinoline (2.0 g) in dry tetrahydrofuran (50 ml) and dry ether (50 ml) at −65°C under dry nitrogen. The solution was stirred at −65°C for 15 minutes and then a solution of dry dimethylformamide (7.0 g) in dry tetrahydrofuran (7.0 ml) was added. The solution was stirred at −65°C for a further 20 minutes and then ethanol (5 ml) was added. The solution was allowed to warm up to 0°C and a saturated solution of ammonium chloride (100 ml) was added. The organic layer was separated and the aqueous layer was extracted with ether. The combined organic layer and ethereal extracts were dried ($MgSO_4$) and evaporated at room temperature under reduced pressure to give crude isoquinoline-5-carboxaldehyde as an oil.

The oil was dissolved in methanol (30 ml) and sodium borohydride (1.70 g) was added portionwise with stirring over 45 minutes. The mixture was stirred for a further 1 hour and then evaporated. Dilute hydrochloric acid (50 ml) was added to the residue and the mixture was extracted with methylene chloride. The aqueous layer was made just alkaline with sodium hydroxide and the mixture was extracted several times with methylene chloride. The combined extracts were washed with brine and dried ($MgSO_4$). Evaporation of the solvent gave crude 5-hydroxymethylisoquinoline as an oil.

The oil was dissolved in dry chloroform (30 ml) and thionyl chloride (1.5 ml) was added dropwise with stirring. The mixture was stirred at room temperature for 2 hours and evaporated to small bulk. The solid was filtered off and dried to give 5-chloromethylisoquinoline hydrochloride (1.1 g), m.p. 204°C(d).

A mixture of finely ground potassium hydroxide (0.60 g), tetrabutylammonium bromide (0.30 g), ethyl *p*-hydroxybenzoate (0.78 g), and 5-chloromethylisoquinoline hydrochloride (1.0 g) in dry tetrahydrofuran (50 ml) was heated under reflux for 4 hours and then allowed to stand at room temperature for 18 hours. The mixture was filtered and the filtrate was evaporated and the residue was suspended in dil. NaOH solution. The mixture was extracted several times with chloroform and the combined extracts were washed with brine and dried ($MgSO_4$). Evaporation of the solvent gave a solid which was crystallized from petrol (b.p. 60—80°) to give 5-(4-carbethoxyphenoxymethyl)isoquinoline (0.60 g), m.p. 106°C.

Analysis %:—

Found:	C, 73.79,	H, 5.59,	N, 4.45.
Calculated for $C_{19}H_{17}NO_3$:	C, 74.25,	H, 5.58,	N, 4.56.

Example 39

5-(4-Carboxyphenoxymethyl)isoquinoline hydrochloride hemihydrate

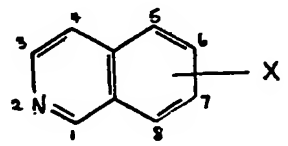
A solution of 5-(4-carbethoxyphenoxy)methylisoquinoline (0.40 g) in acetic acid (1.5 ml) and concentrated hydrochloric acid (1.50 ml) was heated under reflux for 1.5 hours and then cooled. The solid was filtered off and crystallized from methanol/water to give 5-(4-carboxyphenoxymethyl)-isoquinoline (0.16 g), m.p. 270—272°C(d).

Analysis %:—

Found:	C, 62.92,	H, 4.62,	N, 4.45.
Calculated for $C_{17}H_{13}NO_3.HCl.0.5H_2O$:	C, 62.87,	H, 4.66,	N, 4.31.

Claims

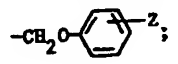
Compounds of the general formula:—



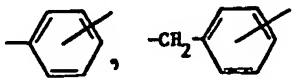
— (I)

wherein

X, which is attached to the 5-, 6-, 7- or 8- position, is a group of the formula —O—Y—Z or



Y is $—(CH_2)_n—$ wherein n is 1, 2, 3, or 4, or a group of the formula:—



or —CH_2—(Het)—;

Het represents a 5 or 6 membered aromatic heterocyclic ring linked to Z by a ring carbon atom;

Z is $—CO_2R^1$, $—CONHR^2$, $—CON(R^3)_2$, $—NHR^4$, $—NHCONHR^5$, —CN, 5-tetrazolyl, 5-oxo-2-pyrazolin-1-yl or 3-methyl-5-oxo-2-pyrazolin-1-yl, with the proviso that when Y is $—CH_2—$(Het)—, Z may also be $C_1—C_4$ alkyl, but may not be $—NHR^4$ or $—NHCONHR^5$;

R^1 is H or $C_1—C_4$ alkyl;

R^2 is H, $C_1—C_4$ alkyl, $C_2—C_4$ alkanoyl, aroyl, $C_1—C_4$ alkylsulphonyl, arylsulphonyl, aryl, aralkyl, or a 5 or 6 membered aromatic heterocyclic ring optionally substituted by one or two $C_1—C_4$ alkyl, $C_1—C_4$ alkoxy, halogen or CF_3 groups;

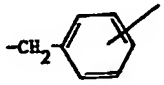
each R^3 is $C_1—C_4$ alkyl or two groups R^3 together with the nitrogen atom to which they are attached form a pyrrolidino or piperidino group;

R^4 is H, $C_1—C_4$ alkyl, $C_2—C_4$ alkanoyl, $C_1—C_4$ alkylsulphonyl, or ($C_1—C_4$ alkoxy)carbonyl; and

R^5 is $C_1—C_4$ alkyl or aryl;

and the pharmaceutically acceptable acid addition salts thereof.

2. A compound of the formula (I) as claimed in claim 1 wherein X is in the 5- position and is $—O—Y—Z$: Y is $—(CH_2)_n$ where n is as defined in claim 1 or a group of the formula:—



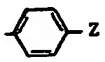
or $—CH_2—$(Het)—; and Z and "Het" are as defined in claim 1.

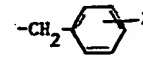
3. A compound of the formula (I) as claimed in claim 1 wherein

X is in the 5- or 7- position; and

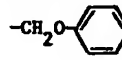
Y is selected from;

(a) $—(CH_2)_nZ$ wherein n is 1, 2 or 3 and Z is $—CO_2H$, $—CO_2(C_1—C_4$ alkyl), $—CONH_2$, $—NH_2$, —CN, —NHCONH ($C_1—C_4$ alkyl), —NHCONH.Phenyl, $—NHSO_2$ ($C_1—C_4$ alkyl), 5-tetrazolyl, or 3-methyl-5-oxo-2-pyrazolin-1-yl;

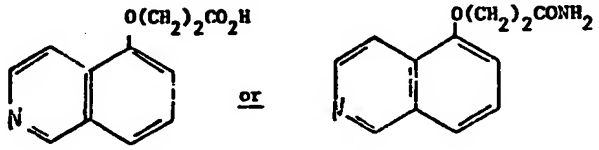
(b)  wherein Z is —CN, $—CONH_2$ or —COOH;

(c)  wherein Z is —CN, $—CONH_2$, —COOH or —CONH(2-pyridyl);

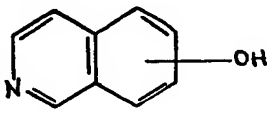
(d) $—CH_2—$(Het)—Z wherein "Het" is pyridyl or thienyl and Z is —COOH, $—COO(C_1—C_4$ alkyl) or $—CONH_2$; and

(e)  wherein Z is —COOH or $—COO(C_1—C_4$ alkyl).

4. A compound of the formula:—



5. A process for preparing a compound of the formula (I) as claimed in claim 1, which comprises reacting a hydroxyisoquinoline of the formula:—

 --- (II)

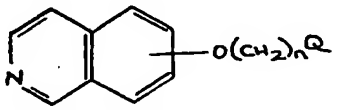
first with an alkali metal base and then with a halide of the formula:—

$$Q—Y—Z \qquad \text{(III)}$$

wherein Y and Z are as defined in claim 1 and Q is Cl, Br or I.

6. A process for preparing a compound of the formula (I) as claimed in claim 1 in which —Y—Z is $—CH_2CH_2CN$ or $—CH_2CH_2COOH$, which comprises reacting a compound of the formula (II) as defined in claim 5 with, respectively, acrylonitrile or acrylic acid.

7. A process for preparing a compound of the formula (I) as claimed in claim 1 in which Y is $(CH_2)_n$ wherein n is as defined in claim 1 and Z is a 5-oxo-2-pyrazolin-1-yl or 3-methyl-5-oxo-2-pyrazolin-1-yl group, which comprises reacting a compound of the formula:—



— (IV)

wherein n is as defined in claim 1 and Q is Cl, Br or I, with 2-pyrazolin-5-one or 3-methyl-2-pyrazolin-5-one, in the presence of an alkali metal base.

8. A process for preparing a compound of the formula (I) as claimed in claim 1 in which Z is —$CONH_2$, which comprises hydrolysing the corresponding compound in which Z is —CN.

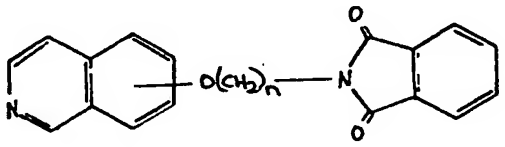
9. A process for preparing a compound of the formula (I) as claimed in claim 1 wherein Z is —COOH, which comprises hydrolysing the corresponding compound in which Z is —CN or —$COO(C_1$—C_4 alkyl).

10. A process for preparing a compound of the formula (I) as claimed in claim 1 in which Z is —$NHCONHR^5$ wherein R^5 is as defined in claim 1, which comprises the reaction of the corresponding compound in which Z is —NH_2 with an alkyl or aryl isocyanate of the formula R^5NCO.

11. A process for preparing a compound of the formula (I) as claimed in claim 1 wherein Z is —NHR^4 wherein R^4 is C_1—C_4 alkylsulphonyl or C_2—C_4 alkanoyl, which comprises reacting the corresponding compound in which Z is —NH_2 with a C_1—C_4 alkylsulphonyl halide or C_2—C_4 alkanoyl halide respectively.

12. A process for preparing a compound of the formula (I) as claimed in claim 1 wherein Z is 5-tetrazolyl, which comprises reacting the corresponding cyano derivative with sodium azide and ammonium chloride.

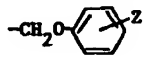
13. A process for preparing a compound of the formula (I) as claimed in claim 1 wherein Y is $(CH_2)_n$ and Z is —NH_2, which comprises reducing the corresponding phthalimido derivative of the formula:—



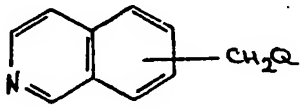
— (V)

wherein n is as defined in claim 1.

14. A process for preparing a compound of the formula (I) as claimed in claim 1 wherein X is

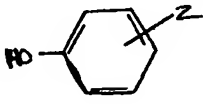


Z being as defined in claim 1, which comprises reacting a compound of the formula:



— (VI)

wherein Q is Cl, Br or I,
with a compound of the formula:—



(VIII)

where Z is as defined in claim 1.

15. A process for preparing a compound of the formula (I) as or a pharmaceutically acceptable acid addition salt thereof as claimed in claim 1, substantially as hereinbefore described in any one of Examples 1 to 39.

16. A compound of the formula (I) as claimed in claim 1 or pharmaceutically acceptable acid addition salt thereof which has been prepared by a process as claimed in any one of claims 5 to 15.

17. A pharmaceutical composition comprising a compound of the formula (I) as claimed in any one of claims 1 to 4 and 16, or a pharmaceutically acceptable acid addition salt thereof, together with a pharmaceutically acceptable diluent or carrier.

Printed for Her Majesty's Stationery Office by the Courier Press, Leamington Spa, 1981. Published by the Patent Office, 25 Southampton Buildings, London, WC2A 1AY, from which copies may be obtained.